Heparin in Acute Myocardial Infarction

Observations Indicating the Potential Advantages of Using It As the Sole Anticoagulant in Therapy

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• **There is a considerable body of experimental evidence that heparin is superior as an anticoagulant to any prothrombin depressing drugs. Furthermore its lipemia-clearing action affords other benefits which result from the removal of fat from the bloodstream. Important among these beneficial effects is the increased tissue and myocardial oxygen consumption which results from the injection of heparin in atherosclerotic patients.**

Because of these advantages of heparin over oral anticoagulants, the use of heparin as the sole anticoagulant for three weeks in patients with severe acute myocardial infarction was evaluated as opposed to the customary therapy where heparin is given for several days and then oral anticoagulants are used. The mortality in the dicoumarin treated group was 38 per cent, as compared with 28 per cent in the patients who received only heparin for three weeks.

DURING THE PAST FEW YEARS a large body of evidence has accumulated that suggests that heparin would be superior to all oral anticoagulant drugs in the therapy of acute myocardial infarction. It appears from the literature that surgeons, more than internists and cardiologists, have been aware of the advantages of heparin. De Takats[7] said that "the treatment of choice in acute thromboembolic disease is by heparin."

The present communication will outline the experimental findings of others supporting this point of view, will summarize the author's own data indicating improved tissue and myocardial oxygenation after injection of heparin in atherosclerotic patients, and finally will present clinical experiences with administering heparin for three to four weeks as the sole anticoagulant in therapy of acute myocardial infarction. In keeping with this concept was Nichol's[25] report that he and his co-workers had the clinical impression that the longer heparin was continued in therapy of myocardial infarction before oral anticoagulants were given, the better were the results.

As an anticoagulant, heparin has many advantages over prothrombin depressing drugs. It is a physiologic substance with a wide margin of safety whereas oral anticoagulants act by poisoning the liver. Heparin acts immediately and is the only anticoagulant which specifically delays clotting. There are few contraindications to its use, and it is rapidly neutralized by protamine sulfate, polybrene or whole blood. Furthermore there is ample evidence that heparin is a more efficient anticoagulant than coumarin drugs. In studies of intravascular coagulation in dogs Wessler[30] noted that heparin, when given so that clotting times were increased to twice those of the controls, effectively prevented clot formation whereas Dicumarol did not unless prothrombin times were dangerously depressed to 1 to 2 per cent of normal. When thromboplastin, which normally initiates clotting, is added to heparinized blood, formation of clots is prevented more efficiently than when it is added to dicumarolized blood.[29] Heparin, since it is an antithrombin, prevents the cycle of thrombus propagation whereas prothrombin depressing drugs do not.[28] The decided increase in platelet adhesiveness that occurs in patients with myocardial and pulmonary infarction, and that predisposes to thrombosis, is promptly decreased by heparin but not by Dicumarol[23] despite adequate hypoprothrombinemia. In addition heparin is effective in patients in whom there is resistance to Dicumarol, as after the use of potassium iodide.[16]

Perhaps of equal or greater importance than its anticoagulant advantages is the fact that heparin rapidly clears serum lipemia and removes fat from the bloodstream, a property not possessed by any of the oral anticoagulants. It has been realized only recently that lipemia, *per se*, is harmful. It increases coagulability of the blood,[13] platelet adhesiveness,[20] plasma viscosity,[27] and red cell aggregation and adhesion.[6] Fibrinolysis is decidedly inhibited after a fat meal,[15] as is other enzymatic activity.[4] Serum lipemia decreased oxygen tension in the ischemic myocardium of dogs and produced anginal attacks in selected patients.[19] Conversely the clearing of lipemia after heparin injection in atherosclerotic persons resulted in temporarily improved ballisto-

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TABLE 1.—*Clotting Time, Arteriovenous (A-V) Oxygen Difference, and Serum Lipoproteins After Intravenous (I.V.) and Subcutaneous (S.C.) Heparin and Dicumarol*

	Clotting Time (Lee-White)	A-V Oxygen Difference (Vol. Per Cent)	Standard Serum Lipoproteins* in mg. Per Cent			
			Sf 0-12	Sf 12-20	Sf 20-100	Sf 100-400
Control	12 min.	3.9	405	45	119	29
10 minutes after 100 mg. I.V. heparin	60 min.	3.8	381	38	20	0
3 hours after 100 mg. I.V. heparin	28 min.	6.1	349	11	0	0
12 hours after 150 mg. heparin S.C. Had 3 doses every 12 hours	Over 45 min.	7.8	311	36	22	0
On Dicumarol 1 week	Prothrombin 25 Per Cent	4.4				

*Sf = Svedberg flotation designation of density.

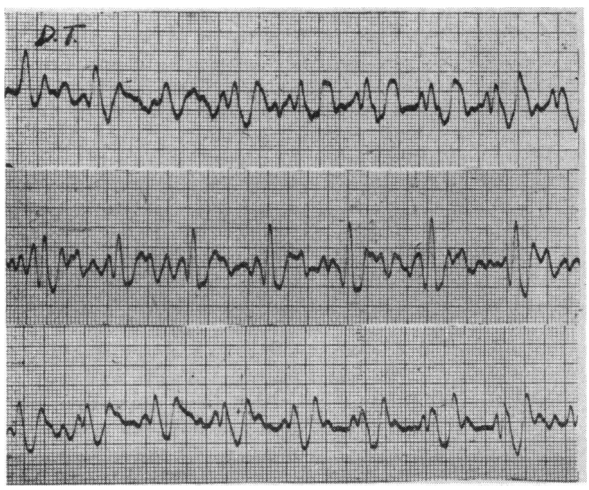

Figure 1.—Records of patient, age 48, with anginal syndrome. *Upper record:* Before heparin, small I and J waves, slurred deep K wave, large L wave, late downstroke pattern. *Center record:* 24 hours after 100 mg. of heparin intravenously, normal pattern. *Lower record:* 72 hours after heparin, record essentially as before heparin.

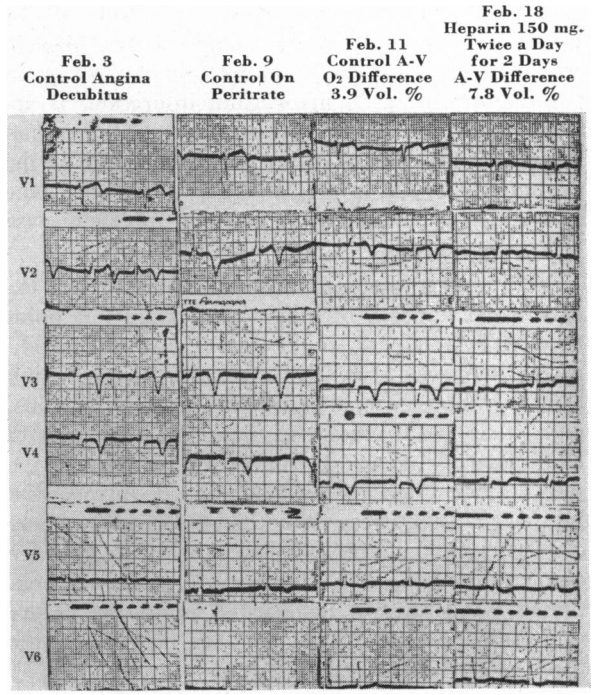

Figure 2.—Electrocardiographic changes associated with decidedly increased arteriovenous (A-V) oxygen differences.

cardiographic patterns[8] (Figure 1), in normalization of previously depressed forearm tissue oxygen uptake with concomitant electrocardiographic improvement of anoxic T waves[12] (Table 1 and Figure 2) and in a pronounced average increase (32.7 per cent) in total oxygen consumption in almost half of 46 patients under basal conditions[9] (Table 2). Saline placebos and Dicumarol had no such effect on tissue hypoxia (Table 3). It appears likely, therefore, that the lipemia-clearing action of heparin in patients with acute infarction, in whom a low fat intake is less effective in reducing lipids than in normal subjects,[26] will result in benefits beyond those obtained from the use of oral anticoagulants.

Finally heparin possesses properties advantageous in the therapy of acute coronary occlusion. It inhibited experimental pulmonary edema,[21] and decreased the incidence of irreversible hemorrhagic shock in dogs.[5] Heparin, at therapeutic levels, increased myocardial contractility, whereas the latter was decreased by Dicumarol.[14] Following myocardial infarction, erythrocyte aggregation sufficient to produce embolization of the conjunctival arterioles was not prevented by adequate prothrombin depression, whereas heparinization prevented a similar phenomenon in patients with malaria.[3] Heparin may also normally function in collagen fiber formation[24] and in the repair of the endothelial intercellular cement.[22]

TABLE 2.—*Summary of Data in 46 Patients After 100 mg. of Heparin Intravenously*

Oxygen Consumption After Heparin	Number of Individuals	Average Change	Initial Oxygen Consumption*
Increased	20	32.7%	174
Decreased	3	15.3%	164
Unchanged	23	....	205

*In ml./minute.

In view of this rather impressive array of evidence indicating the advantages of heparin therapy, its use as the sole anticoagulant for three to four weeks

in the treatment of acute infarction was suggested.[10] Subsequently a comparative study of heparin alone as compared with heparin plus Dicumarol in patients with severe acute myocardial infarction was undertaken. The complete details of that investigation will be published elsewhere,[17*] but the summation of the results obtained is shown in Table 4. Mortality in the total group that received heparin for two or three days and then dicoumarin was 38 per cent; in the patients receiving heparin alone for three weeks, the rate was 28 per cent. The difference in results between the two types of therapy was not statistically significant although it was suggestive of heparin superiority. This was substantiated by the findings in the most seriously ill patients, those with three or more complications on admission. In these subjects the mortality rates were significantly different: For the group treated entirely with heparin, 23 per cent; for those receiving heparin and dicoumarin, 58 per cent.

At this point, it may be well to discuss details of the administration of prolonged heparin therapy in actual practice, and some of the problems encountered. A 50 or 100 mg. dose should be injected intravenously when the diagnosis of infarction is made in order to attain full anticoagulant activity immediately. Subsequently, if the patient is receiving continuous intravenous therapy, 50 mg. of heparin should be given in the infusion tube every four hours. This method requires infrequent laboratory controls. If continuous intravenous drip is not being employed, subcutaneous injection is preferred. This has been made possible by the advent of highly refined concentrated aqueous heparin that is as slowly absorbed as the repository or depot material,[1,11] yet is less expensive, less painful, and easier to administer. In nearly all patients 150 mg. of the concentrated aqueous heparin every 12 hours subcutaneously affords excellent maintenance of anticoagulation effect. In the first two to three days after infarction, slightly larger doses may be needed in a few individuals, as a state of increased coagulability often exists. Frequently, after the first three to four days a dose of 100 to 125 mg. every 12 hours suffices. Ware[28] advocated the use of 100 mg. subcutaneously every eight hours and expressed the belief that with this method it is unnecessary to make frequent determination of clotting time. With either technique it is advisable, however, during the first two days, to measure clotting time once daily by the Lee-White method, just before the next scheduled administration of heparin, primarily to check on the adequacy of the dose. Once a stable anticoagulant level is reached, it is not necessary to determine clotting time so often; perhaps once or twice a week is enough. The peak

*This study was performed at the Los Angeles County General Hospital.

TABLE 3.—*Total Oxygen Consumption (in Milliliters per Minute) After Heparin, After Saline Placebo Intravenously, and After Oral Anticoagulant*

Case	Intravenous	Oxygen Consumption ml./min. Control	After Intravenous Injection 5-10 Min.	2 Hr.	Change* in O_2	After Dicumarol 1 Week
1	Heparin	79	60	97	+23%	
	Saline	83	78	82	—	82
2	Heparin	175	204	253	+45%	
	Saline	202	184	172	—15%	202
3	Heparin	247	313	316	+28%	
	Saline	260	278	262	—	251
4	Heparin	320	275	412	+29%	
	Saline	290	280	274	—	284
5	Heparin	189	224	321	+70%	
	Saline	206	186	202	—	210
6	Heparin	79	171	153	+94%	
	Saline	94	106	127	+35%	110
7	Heparin	63	97	112	+77%	
	Saline	71	82	80	+13%	78
8	Heparin	98	93	125	+27%	
	Saline	92	90	86	—	
9	Heparin	95	85	121	+26%	
	Saline	104	92	88	—	
10	Heparin	179	167	276	+54%	
	Saline	160	171	158	—	
11	Heparin	333	362	440	+32%	
	Saline	320	352	348	+ 9%	
12	Heparin	248	270	266	+ 7%	
	Saline	224	210	213	— 4%	

*Compared with control period.

TABLE 4.—*Mortality Data on Patients Treated with Heparin Only, and Those Treated with Heparin for Two or Three Days and Then Dicumarol*

	Heparin Only			Heparin, Then Dicumarol		
	No. of Cases	No. of Deaths	Death Rate	No. of Cases	No. of Deaths	Death Rate
Total group	100	28	28%	63	24	38%
Patients with 3 or more complications on admission	60	14	23%	19	11	58%

anticoagulant effect is obtained several hours after each injection, but the level is of little concern, as it has been our experience as well as that of the Scandinavian investigators[2,18] that transient clotting times of one to two hours are not dangerous and neutralization measures to shorten the time are not required. The only indication for the use of protamine or polybrene when heparin is given is the occurrence of active major bleeding. Heparin given intravenously is usually neutralized by one ampule of protamine or the newer and more efficient preparation, polybrene, whereas after subcutaneous or intramuscular injection of heparin, several doses of the heparin antagonist drugs may be needed because of the prolonged absorption time of heparin by those routes. When heparin is stopped because of minor bleeding, clotting time should be determined every 6 to 12 hours and the use of heparin resumed (using a smaller dose) when the time has returned to normal. This is desirable because abrupt premature termination of therapy may predispose to thromboembolic complications, which are more hazardous

than the hemorrhagic ones. In the entire series of 100 patients in the Los Angeles County General Hospital study[17] and in 36 private cases in which heparin was used, there were no hemorrhagic deaths.

Heparin is also effective when given intramuscularly in 100 mg. doses every eight hours. However, this mode of administration is more likely to be painful and to produce ecchymosis. Because of their previous experience using the older gel preparations, most nurses, unless carefully instructed, will give heparin intramuscularly, or will use the upper arm for subcutaneous injection. The latter site is inadvisable, for the subcutaneous space is limited in this area. The incidence of local pain and ecchymosis at the injection site is minimized if more concentrated aqueous heparin (200 or 400 mg. per cc.) is given very slowly in the subcutaneous fat tissue above the posterior or lateral iliac crests, using a small bore needle (No. 25 French). With this technique many patients may also be satisfactorily treated at home, using a dose of 250 to 300 mg. once daily. However, the 12-hour dosage schedule is preferred, as it affords more sustained but less pronounced anticoagulation (clotting time of 20 to 60 minutes). Recently Wessler described a simple method for the intermittent administration of drugs intravenously over prolonged periods, using an indwelling polyethylene catheter and a rubber-capped adapter.[31] This procedure can be employed for giving frequent small doses of heparin intravenously without the necessity of repeated venipunctures. It may well be the best technique available, and certainly should be used for sensitive persons who find subcutaneous administration excessively painful.

The only major objection to the routine use of heparin for the entire period that anticoagulant therapy is necessary following thromboembolic disease is the cost. This is partially compensated for by the necessity of more frequent laboratory control tests when prothrombin depressing drugs are prescribed. It is also possible to lower the cost of heparin considerably in most hospitals. Many hospital pharmacists have retained the former charges for heparin in aqueous solution although their costs have been substantially reduced in recent years. They may be induced to lower the price to the patient if the physician explains that he would prescribe heparin for more prolonged periods, rather than oral anticoagulant drugs, if the charges for heparin were reasonable (thus increasing the profit to the pharmacy, which would make more on one vial of heparin than on dozens of tablets).

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